

R E M A R K S

Entry of the Amendment, reexamination, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. §§ 1.114 and 1.111, are thus respectfully requested.

1. Status of the Claims

The status of the claims following entry of the amendments is as follows:

Claims pending: 1, 3-11, and 13

Claims rejected: 1-3 and 7-9

Claims objected: 4-6 and 10-14

Claim canceled: 2, 12, and 14

Claim amended: 1 and 11

Applicants note that the present claim amendments are based on the claims that were amended in the Amendment / Response filed May 24, 2010.¹ Applicants believe that the present amendments fully comply with 37 C.F.R. § 1.121.

2. Support for the Claim Amendments

Applicants amend (1) claim 1 to incorporate elements from claim 2 (now canceled); and (2) claim 11 to incorporate elements from claim 12 (now canceled). Support for the recited “tritium-containing ethyl group (X=C₂H₃T₂)” in claim 1 can also be found at least in original claim 10 and lines 1-7, at page 14 of the Specification (Scheme 5). Applicants do not believe that the amendments add prohibited subject matter that is unsupported by the Specification as filed.

Cancellation of and amendments to the claims have been made without prejudice to or disclaimer of the subject matter contained therein. Applicants reserve the right to file a continuation and/or divisional on any subject matter canceled by way of amendment.

¹ The Advisory Action mailed February 15, 2011 states that the Amendment / Response filed February 2, 2011 “will be entered”... “*if for purposes of appeal.*” Instead of filing an Appeal Brief, Applicants file the Amendment / Response with an RCE.

3. Information Disclosure Statement

Applicants appreciate the Office's acknowledgment of the Information Disclosure Statement (IDS) submitted January 6, 2011.

Applicants submit herewith another IDS for consideration by the Office. Acknowledgement and return with the Office's next communication is respectfully requested.

4. Withdrawn Objections and Rejections

Rejections and objections not reiterated stand withdrawn. *See* 37 C.F.R. § 1.113(b); M.P.E.P. §§ 706.07 and 707.07(e).

5. Rejection under 35 U.S.C. §103(a).

The Office maintains the rejection of claims 1-3 and 7-9 as allegedly obvious over WO 03/000698 ("the '698 publication").

5.1 Claims 1-2 and 7-8

Grounds For Rejection

The Office alleges that "Applicants' claims teach known compounds with the addition of a radiolabel." Office Action, page 3. The '698 publication allegedly discloses a valid reason or suggestion to modify the compounds. *Id.* The Office further alleges that claimed "straight or branched lower aliphatic alkoxy group" includes the methoxy group as shown in the ligand of Scheme 2 of the '698 publication. *Id.*, at 3-4.

The Office further alleges that the '698 publication, at page 29, teaches at least four compounds that only "differ from those encompassed by Applicant's claim 1 in that none are depicted as radiolabeled at the equivalent X-position." Advisory Action mailed February 15, 2011, page 2. The '698 publication allegedly "provides a valid reason to modify these compounds to arrive at their radiolabeled counterparts." *Id.*, at 3. The Office concludes that "the '698 publication discloses compounds which anticipate Applicant's formula (1) but for a radiolabel, discloses a reason to radiolabel these compounds, and discloses an example suggesting radiolabeling the X-position." *Id.*

Arguments

Applicants traverse the rejection to the extent it applies to the amended and un-amended claims. Applicants traverse. “[O]bviousness requires a suggestion of *all* limitations in a claim.” *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 U.S.P.Q.2d 1940, 1947 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974) (emphasis added). The Office must also establish that one of ordinary skill in the art would have had a reasonable expectation of success to practice the claimed invention. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

A. Not All Claim Elements are Taught

Given the present claim amendments, the Office’s rejection is unsupported. The cited reference does not teach or suggest all claim elements. As amended, claim 1 recites, *inter alia*, that the radioactive substituent on the benzoyl group of the compound having the formula (1) is ^{125}I or a tritium-containing ethyl group ($\text{X}=\text{C}_2\text{H}_3\text{T}_2$). Scheme 2 of the ‘698 publication at best may teach preparing radio-labeled methoxy-substituent (-OCH₃). The ‘698 publication does not teach iodine or ethyl group as the substituent on the benzoyl group of the compound having the formula (1). *See* the ‘698 publication, at page 29. Nor does the ‘698 publication teach the *radioactive* substituents (^{125}I and $\text{C}_2\text{H}_3\text{T}_2$). There is no evidence on the record or adduced by the Office that a skilled artisan would have been directed to make or use the presently claimed radioactive substituents (^{125}I and $\text{C}_2\text{H}_3\text{T}_2$). The ‘698 publication does not teach all claim elements. Thus, the Office fails to adduce *prima facie* obviousness, because the cited reference fails to teach or suggest at least the recited radioactive substituents.

B. There Is No Reasonable Expectation Of Success

Even if it were assumed *arguendo* that a skilled artisan would have been motivated by the ‘698 publication to introduce either of the claimed radioactive substituents (^{125}I and $\text{C}_2\text{H}_3\text{T}_2$) into the benzoyl group of a compound having the formula (1), which it does not, a skilled artisan would not have had a reasonable expectation of success to introduce the radioactive substituent at the recited position. The claimed radiolabeled substituents resides at the 4-position (*para*-position) of the benzoyl group, while the *non-radiolabeled* substituents of the compounds

disclosed in the '698 publication spread through all three positions (*ortho*-, *meta*- and *para*-positions). See Office Action mailed November 24, 2009, pages 3-6. There is no suggestion to add a radiolabeled group to the 4-position in particular, over any other position, let alone an expectation that such a modification would have had an expectation of success.

The Office is directed to the paragraph bridging pages 9-10 of the Specification:

TBOA occurs as four stereoisomers and the (2S,3S) compound shows the strongest activity among them. The substituent on the benzoyl ring may be located at three positions, i.e., *ortho*-, *meta*- and *para*-positions. *Studies on the structure-activity-relationship of these compounds clarified that the para-compound shows the strongest activity.* Therefore, in the following synthesis scheme the introduction of a radioactive substituent is shown by taking compounds having a (2S,3S)-configuration in the aspartic acid and having the substituent at the *para*-position on the benzoyl, though all isomers having different substitution or configuration manners are included in the scope of the present invention.

(emphasis added). At the time, there was no indication, absent testing, that substitution at one position over another would have produced a better activity.

In fact, the '698 publication describes that the strongest activity results from the *meta*-position of the amino group on the benzene ring, *not* the *para*-position. See page 8, lines 7-17 of the '698 publication. Given the teachings of the '698 publication, a skilled artisan would *not* have been directed to even try to modify the *para*-position. There is no evidence on the record or adduced by the Office that (1) there is guidance in the art to make and/or use the claimed compounds; and (2) a skilled artisan would have been motivated to do so with a reasonable expectation of success.

C. The Claimed Compounds and Methods Offer Unexpected Advantages

Further, the claimed compounds and methods offer unexpected advantages. Scheme 2 of the '698 publication teaches preparing radio-labeled methoxy-substituent, while the recited radioactive substituent is ^{125}I or $\text{C}_2\text{H}_3\text{T}_2$. The binding activities (shown as IC_{50}^2) of these radio-labeled substituents are shown below:

² See Specification, Table 2, page 25; the '698 publication, Table 1, page 37. The IC_{50} was determined as the ability to inhibit the uptake of [^{14}C]-glutamic acid by human EAAT2 and EAAT3 stably expressed in MDCK (Madin-Darby canine kidney) cells or transiently expressed in COS-1 cells. See Specification, paragraph bridging pages 24-25.

- 1) $IC_{50} = 12$ nM for the radio-labeled methoxy-substituent of the '698 publication;
- 2) $IC_{50} = 4.8$ nM for the recited ^{125}I -substituent; and
- 3) $IC_{50} = 3.2$ nM for the recited $C_2H_3T_2$ -substituent.

See the '698 publication, Table 1, page 37; and Specification, Table 2, page 25, and Fig. 9. The binding activity of either the recited radioactive compound is much higher than that of the methoxy-substituent as taught in the '698 publication. Thus, both the recited radioactive compounds are "high-affinity" ligands for the glutamate transporter. These high-affinity ligands are suitable for the development of a "binding assay," which is superior to the conventional "uptake assay." See, e.g., Shimamoto et al., 71 MOL. PHARMACOL. 294 (2007), "Discussion" at pages 299-301 ("Shimamoto") (enclosed as Exhibit II in the Amendment / Response filed May 24, 2010); *see also* Specification, lines 6-18 at page 5.³ Additionally, the tritium gas labeling process is capable of producing purer products with a higher yield, compared to the methylation of a phenolic hydroxyl group as shown in Scheme 2 of the '698 publication. *See id.*, right column under "Material and Methods," page 295.

Given the above discussion, the claimed compounds and methods offer unexpected advantages over the teachings of the '698 publication. In view of at least these arguments, amended claim 1 is nonobvious over cited references. Dependent claims 7-8 are likewise nonobvious for at least the same reasons. Claim 2 stands canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

³ "By radio-labeling such a selective and high-affinity ligand of the transporter, a specific binding even in a trace amount could be detected. Thus, such radio-labeling would bring about a significant contribution in the field of drug searching based on binding experiments to screen for novel ligands and isolate novel proteins. It would also be expected that the distribution and expression of glutamate transporter and the level of its ability to take up glutamate could be visualized with the use of autoradiography and positron emission tomography (PET) techniques. However, no compound usable in the detection of specific bindings or the visualizing techniques has been known from the viewpoint of satisfactory affinity and selectivity."

5.2 Claim 9

Grounds For Rejection

The Office alleges that claim 9 is obvious, because “the ‘698 publication teaches that its radiolabeled ligands are useful for identification of transporter proteins which, as demonstrated throughout the publication, include glutamate transporter proteins.” Office Action, page 6.

Arguments

Applicants traverse. Claim 9 depends indirectly from claim 1. Claim 1 as amended is nonobvious for at least the reasons discussed in Section 5.1 *supra*. Therefore, claim 9 is similarly nonobvious. Additionally, there is no teaching that would have led a skilled artisan to have identified and used the claimed compounds to identify or characterize glutamate transporter proteins. Given at least these arguments, claim 9 is nonobvious over cited reference. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claim 9.

5.3 Claim 3⁴

Grounds For Rejection

The Office alleges that the Y group recited in Claim 3 can be an organometallic group, which allegedly includes the *tert*-butyldimethylsilyl (TBS) group disclosed at Scheme 2 of the ‘698 publication. Office Action, page 6.

Arguments

Applicants traverse. The Office’s rejection is unsupported, because the Office mischaracterizes the term “organometallic group.” The term “organometallic group” refers to a chemical group containing bonds between a carbon atom and a metal atom. *See, e.g.*, “Organometallic Chemistry” *available at* http://en.wikipedia.org/wiki/Organometallic_chemistry (“Organometallic chemistry is the study of chemical compounds containing bonds between

⁴ The Office listed claim 3 as one of the “Claim(s) objected to” in the Advisory Action mailed February 15, 2011. The Office apparently is persuaded by Applicants’ arguments presented in the Amendment / Response filed February 2, 2011, so that the Office must have objected to claim 3 as dependent from a rejected base claim. As the Amendment / Response filed February 2, 2011 “will be entered”... “*If for purposes of appeal*,” Applicants present the arguments of Amendment / Response filed February 2, 2011 anew.

carbon and a metal.”). The *tert*-butyldimethylsilyl (TBS) group, however, is a commonly used protecting group containing a silicon atom. *See, e.g.*, “Silyl ether” *available at* http://en.wikipedia.org/wiki/Silyl_ether. The silicon atom is *not* a metal atom. Thus, the recited organometallic group differs from the TBS group disclosed in the ‘698 publication. There is no evidence on the record that the ‘698 publication teaches all elements of claim 3. Without all claim elements taught, there can be no expectation of success that the a skilled artisan would have made or used the claimed product predictably.

Given at least these arguments, claim 3 is nonobvious over the cited reference. Applicants respectfully request withdrawal of the rejection and allowance of claim 3.

6. **Claims Objection**

The Office objects to claims 4-6 and 10-14 as allegedly depending from a rejected base claim. Office Action, page 7.⁴ As discussed in Section 4 above, amended claim 1—the base claim—is nonobvious over cited reference. Claims 12 and 14 stand canceled, mooting the objection. Accordingly, Applicants respectfully request withdrawal of the objection and allowance of the claims.

CONCLUSION

In view of the above arguments and amendments to the claims, Applicant submits that the claims are in condition for allowance and respectfully request reconsideration and timely allowance of the claims.

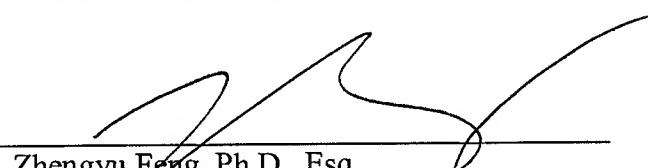
Should the Office have any questions or comments regarding Applicant's amendments or response, please contact Applicant's undersigned representative at (202) 230-5119.

Furthermore, please direct all correspondence to the below-listed address.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0573. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,

Date: September 1, 2011 By:


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